Remarks:

Claims 11 and 58 have been amended to recite that antibodies are peripherally administered to a patient. Peripherally administered antibodies must cross the blood brain barrier to reach amyloid deposits. The amendment is supported by the specification at *e.g.*, p. 104, line 28 to p. 105, line 18 showing that peripherally administered antibodies can cross the brain barrier into the CNS and p. 53, lines 22-25 providing representative examples of routes of peripheral administration. Claims 11 and 58 have also been amended to recite the NAC fragment as suggested by the Examiner. No amendment should be construed as acquiescence in any ground of rejection. Applicant uses the paragraph numbering of the office action in responding to the Examiner's comments.

¶3. Priority

The Examiner alleges that US Application No. 09/580,015 provides no disclosure of antibodies binding to synuclein NAC. In response, the Examiner's attention is drawn to p. 98, second paragraph and p. 19, first paragraph. Nevertheless, the issue of priority to US Application No. 09/580,015 is moot in view of the Examiner having acknowledged priority to earlier application US Application No. 60/137,010, filed June 1, 1999.

¶5. Claims 11, 58 and 74-81 stand rejected on the basis that the claims should refer to "the" rather than "a" NAC fragment. The claims have been amended as suggested by the Examiner.

¶6. Claims 11, 58, and 74-81 stand rejected for alleged lack of enablement on several grounds which will be discussed in turn.

First, the Examiner alleges that the declaration of Dr. Koller is not relevant because it does not describe administration of antibodies or mention the NAC fragment of alpha-synuclein. In response, these comments miss the point for which the declaration was offered. The human clinical evidence discussed by Dr. Koller shows that one of the agents described in

the specification (*i.e.*, Aβ42) as having pharmacological activity in reducing or eliminating plaque burden in the PDAPP mouse model also has useful clinical activity in the human trial. Given this correlation, it is all the more likely that other agents that can clear plaques, such as antibodies to alpha synuclein, also confer clinically useful benefits in humans.

Next, the Examiner alleges that Dodard teaches that the "ability to remove plaques from the brain is divorced from cognitive improvements" (office action at p. 4, first paragraph). Based on this allegation, the Examiner infers that the present demonstration that antibodies to NAC reduce plaques *ex vivo* is not a predictor of clinical utility. In response, Dodard merely proposes that cognitive benefits can be achieved without removing plaques by clearing soluble Aβ. Dodard does not say, nor does his proposal imply, that removal of plaques cannot also lead to cognitive benefits. Indeed, following his proposal, Dodard reviews several prior reports in which cognitive benefits have been accompanied by a reduction in plaque (p. 455, paragraph bridging cols. 1 and 2). Moreover, it has subsequently been reported that a human Alzheimer's patients immunized with Aβ1-42 who generated antibodies to amyloid plaques, showed significantly slower rates of decline of cognitive functions as compared to patients not developing such antibodies (Hock *et al.*, *Neuron*, 38, 542-554 (2003), cited as cited no. 534). For these reasons, Dodard merely teaches an additional mechanism by which a cognitive benefit may be obtained, but does provide any teaching inconsistent with obtaining a cognitive benefit from removal of plaques, the principal pathological feature of Alzheimer's disease.

The Examiner discounts the case law of *In re Brana* as inapplicable because the *ex vivo* assay disclosed in the present specification is not reasonably predictive of treatment of Alzheimer's disease. However, as discussed above, the Examiner's position is based on an incorrect assumption that Dodard teaches that clearing plaques does not result in any therapeutic benefit.

Finally, the Examiner finds particular fault with claim 58 and dependent claims in reciting "prophylactically treating." It appears that the Examiner is construing "prophylactically treating" as not merely including but requiring complete prevention. However, it is not apparent why the Examiner is construing the term in this way, because it is clear from the specification

that reducing risk or delaying onset of disease are also contemplated by this term (*see, e.g.*, p. 23, lines 23-27). If the rejection is maintained, applicant would appreciate clarification of the Examiner's position.

¶7. Claims 11, 58, 74-75 and 78-79 stand rejected as obvious over Masliah, Becker and Solomon. Masliah is alleged to teach treatment of Alzheimer's disease using antibodies that bind to NAC. Becker is alleged to teach treatment of Alzheimer's disease using antibodies that bind in a β-sheet conformation. Solomon is alleged to each that antibodies binding to residues 8-17 and 1-28 are able to inhibit aggregation of Aβ into its toxic aggregated forms, thus guiding selection of antibodies for use in the methods of Becker. The Examiner takes the view that it would have been obvious to co-administer antibodies binding to NAC as taught by Masliah with antibodies binding to within residues 1-28 of Aβ for treatment and prophylaxis of Alzheimer's disease with a reasonable expectation of success. The Examiner cites MPEP § 2144.06 for the proposition that co-administration two compounds each known to be effective for the same purpose is prima facie obvious in lieu of any motivation to combine the teachings of the references.

Applicants disagree that MPEP § 2144.06 is applicable not least because the cited art did not establish antibodies to alpha synuclein were effective for treating Alzheimer's disease, particularly when peripherally administered, as recited in the amended claims. As noted in the previous response, Masliah twice expresses doubt that antibodies can cross the blood brain barrier (p. 5 last paragraph and p. 41 last paragraph). Masliah provides no data to indicate that antibodies to NAC can cross the blood brain barrier, or that they are effective to treat Alzheimer's disease with or without crossing the blood brain barrier. Moreover, in alleging lack of enablement, the Examiner has expressed the view that even with the benefit of evidence provided in the present application, use of antibodies to NAC to treat Alzheimer's disease was unpredictable. This evidence includes a demonstration that an antibody to NAC can clear plaques in an *ex vivo* model, evidence that results from the *ex vivo* model correlate with plaque removal *in vivo* (*see, e.g.*, specification at pp. 113-117), and evidence that antibodies to an amyloid component (*i.e.*, Aβ) do cross the blood brain barrier in sufficient amounts to clear

plaques (*e.g.*, p. 104, line 28 to p. 105, line 18). Given that Masliah does not provide any evidence at all that antibodies to NAC (or to any other amyloid component) can cross the blood brain barrier, exert any effect on plaques or otherwise treat Alzheimer's disease, and that before the priority date of the invention Alzheimer's disease was regarded as untreatable disease, it cannot reasonably be said that Masliah established that antibodies to NAC are useful to treat Alzheimer's disease by peripheral administration.

Absent teaching in the prior art that antibodies to NAC were useful to treat Alzheimer's disease by peripheral administration, MPEP § 2144.06 is inapplicable, and Masliah cannot be combined with the other cited references.

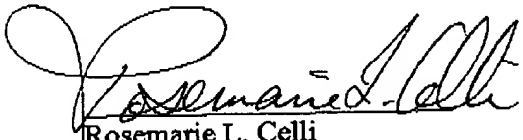
Applicant also disagrees that sufficient motivation has been identified to combine Becker with Solomon. As the Examiner has noted Becker discusses various assays to identify an antibody binding to Aβ in beta sheet formation. However, Becker does not identify such an antibody or its epitope specificity. Absent any information on epitope specificity suitable for use in the methods of Becker, the artisan would not know that antibodies binding to epitopes within Aβ 1-28 or Aβ 8-17 as discussed by Solomon were suitable for use in Becker's methods.

For these reasons, withdrawal of the rejection is respectfully requested.

¶8. Claims 77 and 81 stand rejected as obvious over Masliah, Becker and Solomon as applied to claims 11, 58, 74, 75, 78 and 79 as set forth in paragraph seven of the office action. Claims 77 and 81 are patentable for the same reasons stated for above for independent claims 11 and 58. For these reasons, withdrawal of the rejection is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-625-8100.

Respectfully submitted,



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